Docket No. 600-1-291CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Albert et al. EXAMINER: Nickol, Gary B.

SERIAL NO.: 10/014,877 ART UNIT: 1642

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TITLE: METHODS FOR USE OF APOPTOTIC CELLS TO DELIVER ANTIGEN TO DENDRITIC CELLS FOR INDUCTION OR TOLERIZATION OF T CELLS

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 16 2005.

Loretta Kavanagh
(Name of person Depositing Mail)

Loretta Kavanagh 5/16/05
(Signature and Date)

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF MATTHEW ALBERT, M.D., PH.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Matthew Albert, M.D., Ph.D. do hereby declare as follows:

1. I am a Faculty member in the Department of Immunology at Institut Pasteur, Paris having received my Ph.D. degree in Immunobiology from The Rockefeller University in 1999 and my M.D. degree from Cornell University Medical College in 2000. After that I was a postdoctoral fellow at The Rockefeller University while completing a Clinical Pathology Residency at The New York Presbyterian Hospital.

2. My full curriculum vitae is attached hereto as Exhibit A.

3. My principal area of research is Dendritic Cell Immunobiology and Tumor Immunity, and among other positions I serve as a reviewer in numerous scientific journals including *Science, Nature Immunology, Immunity, PNAS.*

4. I have reviewed the disclosure of the present application, entitled "METHODS FOR USE OF APOPTOTIC CELLS TO DELIVER ANTIGEN TO DENDRITIC CELLS FOR INDUCTION OR TOLERIZATION OF T CELLS" and have also reviewed a reference by Engleman et al. WO94/02156, entitled METHODS FOR USING DENDRITIC CELLS TO ACTIVATE T CELLS. My laboratory has conducted work in this area of research for many years. The means by which Engleman et al. activate T cells is different from the means for activating T cells presented in the current patent application.

5. More importantly, the work presented by Engleman et al. does not take into account the fact that there is a distinct difference between irradiating cells with the intent of sterilizing them for human use (killing adventitial adgents), irradiating cells to make the cells necrotic, as compared to irradiating cells to induce apoptosis. There are distinct advantages of cross-presenting antigen in the context of an apoptotic cell, whereas the same does not hold true for use of a necrotic cell. This is clearly pointed out in the present patent application on page 46, lines 23-33, continuing on to page 47, lines 0-7.

6. Apoptosis is a live, active cell process. Our laboratory has demonstrated that active proteolysis is necessary in the apoptotic cell to allow exogenous antigen cross-presentation (see the enclosed pre-print of a paper entitled "Apoptotic Cells Deliver Processed Antigen to Dendritic Cells for Cross-Presentation" in PLoS Biology, June 2005, Volume 3, submitted herewith as Exhibit B). This obviously would not work for necrotic cells. Furthermore, apoptosis inhibitors, such as Z-VAD, block T cell activation even in the presence of UV irradiation (see the present patent application on page 46, lines 4-22). In addition, my research has demonstrated that only specific forms of death activate T cells, that is, apoptosis, but not necrosis.

7. Without providing the type of irradiation and the exact doses of irradiation (gamma or otherwise), it would be difficult, if not impossible, to predict whether one is inducing apoptosis or necrosis. The present patent application clearly defines those conditions, and furthermore, provides proof that the cells were apoptotic. These conditions are

clearly missing from the Engleman et al. reference. One may assume that Engleman et al. were using gamma irradiation, since it is well known in the field that gamma irradiation induces necrotic death under many conditions, but there is no teaching of this in the Engleman et al. publication. Thus, Engleman et al. do not teach whether they induce necrosis or apoptosis.

8. Engleman et al. could not have known to titrate the exact doses of irradiation for the purpose of inducing apoptosis, rather than necrosis for presenting antigen to dendritic cells. It was not until the work of the present patent application that such specific conditions were made known.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18 of the U.S. Code, Section 1001, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: May 16, 2005

Matthew Albert, M.D., Ph.D.

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